REMARKS

Reconsideration and withdrawal of the rejections as set forth in the Office Action mailed April 10, 2003 is respectfully requested.

Claims 86 and 93 are amended, and claims 1-86 and 94-99 are canceled; as a result, claims 86-93 and 100-105 are now pending in this application.

§101 Rejection of the Claims

Claim 95 was rejected under 35 USC § 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. The cancellation of claim 95 moots this rejection.

§112 Rejection of the Claims

Claim 93 was rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 93 has been amended to correct the improper dependency. Withdrawal of the rejection of claim 93 is respectfully requested.

§103 Rejection of the Claims

Claims 86-105 were rejected under 35 USC § 103(a) as being unpatentable over Giralt et al (VIIth Int'l Multiple Myeloma Proceedings, Abstract No. 0033, 1999, page 117) or Giralt et al. (Blood, 1999, Abstract #3133, page 709a) in view of Bugaj et al. (US Patent No. 4,707,353) in further view of Kaplan et al. (US Patent No. 4,853,209), Bayouth et al. (Journal of Nuclear Medicine, 1995, 35 (5), 730-737), and Simon et al. (US Patent No. 5,300,279), This rejection is respectfully traversed.

Enclosed and listed on PTO Form 1449 are copies of the two Giralt et al. abstracts, which are the only primary references cited by the Examiner. The abstracts are cited to make the cover and the index of record. Giralt et al. (VIIth Int'l Multiple Myeloma Proc., Abstract 033, page 117, is taken from an abstract book dated September 1-5, 1999. Giralt et al., Blood, 709a,

Abstract #3133 was published in an issue of Blood (99 (10) Supp. 1) dated November 15, 1999. (In fact this abstract is properly cited as Champlin et al.)

The Examiner is requested to note that these references are only potentially citable against the present claims under 35 U.S.C. § 102(a), as they were published within a year of the filing date of the PCT application, US/00/16052, that is the parent application to the U.S. application, and that was filed on June 12, 2000. This PCT application claims priority to three U.S. provisional filings, including Serial No. 60/149,821, filed August 19, 1999.

Claims 86-93 and 100-103 are fully supported by the specification of this provisional application. For the convenience of the Examiner, support for some of the primary elements of the claims is outlined on Table 1, below.

Table 1

Claim Element	Supported in 60/149,821 at:
Bone-associated cancer	Claim 91
Hydration of patient	Example 12
^{166}Ho-DOTMP	Page 6, line 8
Radioprotectant	Claim 101
20-60 Gy dose	Page 5, line 22
200 mg/m^2 melphalan	Claims 25, 27
No TBI	Page 22, lines 11-13
Multiple Myeloma	Claim 34
Metastatic Breast/Prostate Cancer	Claims 35-36
Ewing's sarcoma	Claim 31
Ascorbic acid/Gentisic acid	Page 14, line 20
35-75 mg/ml ascorbic acid	Claim 102
pH 7-8	Claim 108
20-30 Gy dose	Table 1, page 10

Therefore, it is respectfully submitted that the Giralt et al. abstracts are not available as prior art citable against the present claims. Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

To the extent that the Examiner may consider re-formulating the rejection in a non-final second rejection, the Examiner is requested to consider the following comments about the secondary references.

The Bugaj et al. patent (U.S. Pat. No. 4,707,353) discloses a mixture of tin metal and a stabilizing compound, such as gentisate or aseorbate, that forms a useful technetium imaging agent when technetium is added to it, and reduced by the stabilizer and the tin (claim 1). No role is ascribed to the stabilizing compound in actually stabilizing a complex between technetium and the optional "tissue specific carrier." The extensive list of tissue-specific carriers does not include DOTMP. In fact, the specification specifically reaches away from the use of substantial amounts of ascorbate as a stabilizing compound when optional "tissue-specific carriers," such as organophosphonates are also employed:

> As is known in the literature, such stabilizing compounds as ascorbic acid can chelate/complex with technetium and cause it to be deposited in soft tissue of the body. Thus, it will be appreciated that the amount of stabilizer included in the instant compositions should not be so great as to overshadow the tissue directing affects of the particular tissue-specific optional carriers . . . [Col. 6, line 13-20].
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> It has been found that stabilizer concentrations greater than about 0.1% interfere with the formation of an acceptable imaging agent. Accordingly, for most purposes where a stabilizer is dissolved in a pertechorate solution, a concentration of no greater than 0.1%, preferably no more than about 0.05% by weight is suitable.

In contrast, the preferred about of stabilizer recited in the present claims is 35-75 mg/ml, or 3.5-7.5%.

Furthermore, one of ordinary skill in the art would not be motivated by the Bugaj disclosures, which is specifically directed to technetium-based imaging compositions and the need to reduce technetium pertectnate *in situ,* to add ascorbate to a ^{166}Ho-based compound, such as ^{166}Ho-DOTMP. As disclosed at page 13 and as shown in Table 3, ascorbic acid effectively prevents degradation of the DOTMP chelator by the ^{166}Ho for up to at least 48 hours, thus greatly enhancing the utility of the dosage form. The general disclosure in the '353 patent that labeled impurities may be reduced does not explain why the use of ascorbate in a technetium-based imaging system would render obvious the use of ascorbate with a different chelated radioisotope.

The Bayouth et al. paper discloses a Phase 1 clinical trial in which six multiple mycloma patients were given 519 mCi to 2.1 Ci of ^{166}Ho-DOTMP. The study does not disclose the use of high dose melphalan with the ^{166}Ho-DOTMP and, in fact, discusses the lack of success using chemotherapy. See p. 730, col. 1. This paper also does not disclose employing pre-hydration of the patients or using a stabilizing agent for the complex.

Kaplan, et al (U.S. Pat. No. 4,853,209) discloses the use of certain aliphatic ^{166}Ho complexes to suppress bone marrow, but does not disclose or suggest the use of cyclic polyaminophosphonates such as DOTMP, as chelators for ^{166}Ho.

Simon et al (U.S. Pat. No. 5,300,279) also discloses certain aliphatic ^{166}Ho complexes to treat calcific tumors or for relief of bone pain. It does not disclose or suggest the use of ^{166}Ho complexed with a cyclic polyaminophosphonate ligand such as DOTMP.

Finally, the Examiner is requested to note that the Giralt et al. abstracts represent studies supported by NeoRx, Inc., the assignee of the present application, and inventors named on the present application are named as co-authors on the abstracts. Thus, it was applicants who combined high dose melphalan chemotherapy with ^{166}Ho-DOTMP to achieve an unexpected high response rate in a particularly intractable cancer (see pages 43-46). As is disclosed at page 46, the complete response rate for previously-treated patients is only 5-25% using conventional follow-up therapy. On the other hand, the abstracts disclose a 53-60% complete response rate across all dosages and Example 11 discloses a complete response rate of 45%. Recent data from a larger patient population indicated a complete response rate of 35% across all doses using Ho-DOTMP. Therefore, it is respectfully submitted that Applicants are entitled to rely on the clinical results presented in Example 11 as compelling evidence of the unexpected success of this combination therapy. See, e.g., In re Hyson, 172 USPQ 339 (CCPA 1972), In re Clinton, 188 USPQ 365 (CCPA 1976) (data in specification considered to rebut allegation of obviousness of claims).